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Docket No: 2136/0K111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Pere RISTOL DEBART, Francisco RABANEDA GIMENEZ, and Ma Teresa Lopez HERNANDEZ

Serial No.: 10/052,324 Art Unit: 1645

Confirmation No.: 1187

Filed: 17 January 2002 Examiner: To Be Assigned

For: PROCESS FOR THE PRODUCTION OF VIRUS-INACTIVATED HUMAN GAMMAGLOBULIN G

EXHIBIT A:
MARKED-UP COPY OF AMENDED CLAIMS AND PARAGRAPHS

SUBMITTED PURSUANT TO 37 C.F.R. § 1.121(b)(1)(iii) and § 1.121(c)(1)(ii)

***IN THE SPECIFICATION*:**

Amend Table 1 on page 28 of the specification as follows:

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Table 1

Parameter	No. [Of] of process batches				
	9002	9003	0001	0002	0003
Protein (%)	4.6	4.5	4.7	4.8	N.D.
Turbidity (NTU)	3.3	3.3	3.0	3.1	2.8
Sorbitol (%)	4.75	4.85	4.9	N.D.	N.D.
Purity (%)	100	99.2	99.7	99.8	99.9
Polymer (%)	0	0	0	0	0
Fractions (%)	0	0	0	0	0
PEG (ppm)	164	311	224	N.D.	N.D.
Polysorbate (ppm)	<30	<30	34	<30	40
TNBP (ppm)	<3.6	<3.6	<3.6	<3.6	<3.6
PKA (IU/ml)	<2.8	<2.8	<2.8	<2.8	<2.8
ACA (CH50/mg Ig)	0.68	0.76	0.75	0.66	0.63
IgA (mg/ml)	<0.003	<0.003	<0.003	<0.003	<0.003
IgM (mg/ml)	<0.002	<0.002	<0.002	<0.002	<0.002

Amend Table 3 on page 32 of the specification as follows:

Table 3

Process No.	No. [Of] of Washing Volumes (in the TFF)	Concentration [Of] of Polysorbate in final product 5% IVIG (ppm)
9003	5	<30
8006	4	50
8007	2.5	200

Amend Table 6 on page 38 of the specification as follows:

Table 6

BATCH No.	% OF POLYMERS (OR HIGH MOLECULAR WEIGHT AGGREGATES)			TURBIDITY (NTU)	
	Before pasteurising	After pasteurising	After SD	Before Pasteurising	After pasteurising
9002	n.d.	1.23	N.D.	1.5	1.6
9003	n.d.	1.16	1.97	1.4	1.8
0001	n.d.	1.04	1.19	5.9	1.8
0002	n.d.	1.21	1.30	2.3	2.4
0003	n.d.	1.35	1.15	1.7	2.0

Amend Table 7 on page 40 of the specification as follows:

Table 7

LOADING [CHARGING] RATIO (g of fraction II+III / ml of resin)	LOADING [CHARGING] TIME (hours)	PURITY OF EFFLUENT (electrophoresis)		(%) RECOVERY OF GAMMAGLO-BULIN (2)
		Albumin (1)	gamma (%)	
4.0	12.15	(+)	97.2	97
2.5		(-)	98.7	95
2.25		(-)	98.3	105
1.25		(-)	97.7	97
0.875		(-)	100	98
0.625		(-)	100	100
1.65	6	(+++)	85.6	n.d.

Amend Table 9 on page 43 of the specification as follows:

Table 9

SORBITOL (%)	PROTEIN (%)	Adjustment to pH 4.0 at 20°C-25°C		Adjustment to pH 4.0 at 2°C-8°C
		Aggregates % (after incubation at pH 4)	Aggregates % (after pasteurising)	Aggregates % (after incubation at pH 4)
5	0.25	N.D.	N.D.	n.d.
5	1	0.31	0.57	n.d.
5	2	0.34	0.64	N.D.
5	2.5	N.D.	N.D.	n.d.
5	3	0.37	1.01	N.D.
5	4	0.93	1.57	N.D.
5	5	0.83	1.81	0.43
5	5	0.86	3.50	
10	5	0.15	0.83	
20	5	0.10	N.D.	
33	5	n.d.	0.70	

Amend Table 10 on page 45 of the specification as follows:

Table 10

SORBITOL [SORBITOL] (%)	PROTEIN (%)	TIME AT [PH 4] pH 4 (hours)	Aggregates % (after treatment at pH 4)	Aggregates % (after pasteurisation)
5	2.5	1	n.d.	0.35
5	2.5	2	0.30	0.59
5	2.5	4	n.d.	0.32
6	3	0	0.11	0.36
6	3	1	0.07	0.31
6	3	4	0.07	0.41
6	3	8	0.40	1.11
6	3	12	0.43	1.18
6	3	24	0.15	0.58

Amend Table 11 on page 46 of the specification as follows:

Table 11

(%) PROTEIN	[Ph] pH	(%) POLYMERS	(%) DIMERS
2.5	5.52	0.46	4.36
2.5	5.03	0.35	3.49
2.5	4.72	0.30	3.31
2.5	4.51	0.45	3.34
5	4.2	4.89	4.54
5	4.0	14.42	5.60
5	3.8	24.51	6.23

Amend Table 13 on page 49 of the specification as follows:

Table 13

CONCEN-TRATION OF PEG (%)	pH	% POLYMER IN THE STARTING IVIG SOLUTION	CONCEN-TRATION OF SORBITOL (%)	PRESENCE OF PRECI-PITATE (1)	(%) RECOVERY OF PROTEIN IN THE FILTRATE (2)
3.0	8.0	n.d.	0.4	YES (+++)	N.R.
3.0	8.0	n.d.	5	YES (+)	N.R.
3.0	8.0	n.d.	10	NO (-)	N.R.
3.0	8.0	3.97	9.4	YES (+++)	83.6
3.0	8.0	3.97	13.0	YES (+++)	92.2

IN THE CLAIMS:

Amend claims 20, 24, 42 and 44-46 as follows:

20. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to claim 19 in which the filtered effluent is [pasteruized] pasteurized in the presence of a [sugar alcohol] sugar-alcohol.

24. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to claim 23 in which, before said treatment with solvent/detergent, the pasteurised effluent is diluted with water for injection so that:

(a) the concentration of sugar alcohol is 25% (w/w) or less, and

(b) the concentration of protein is between 1% and [3#] 3% (w/v).

42. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to [claim35] claim 35, further comprising steps of:

(a) adding an alkali to the acid solution so that the pH is adjusted to between 7.5 and 8.5, and

(b) precipitating and separating insoluble high molecular weight aggregates from the pH adjusted solution.

44. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to claim 42 further comprising, after separating insoluble high molecular weight aggregates from the pH adjusted solution, diafiltration and concentration of the solution, pH adjusted to 4.0 - 4.8, through ultrafiltration membranes of 100 kDa nominal molecular cut-off and at a transmembrane pressure below 1.2 bar.

45. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to claim 44, wherein the solution is concentrated to a protein concentration of 1% to 3% (w/v) and pH adjusted to 4.4 - 5.0.

46. (Once amended) A method for the production of virus-inactivated human gammaglobulin G according to claim 44, further comprising steps of:

(a) heating the solution [to] at between [20 and 25] 25 ± 5 ºC; and

(b) nanofiltration of the solution through membranes having a nominal pore size of 50 nm or less.

***IN THE ABSTRACT*:**

Amend the Abstract of the Disclosure as follows:

ABSTRACT

Process for the production of virus-inactivated human gammaglobulin G.

The gammaglobulin is extracted from a fraction isolated by fractionation with ethanol in the presence of a carbohydrate, and after reducing the content of contaminants with PEG, it is applied to an anionic resin exchange column, an effluent being obtained in which the PEG content is subsequently reduced by ultrafiltration and which is concentrated in order to carry out sequentially an optional treatment at an acid pH and at least one of the following steps of viral inactivation, consisting of pasteurisation and a treatment with solvent/detergent, the product afterwards being precipitated and washed with PEG in order to eliminate any chemical viral inactivation reagents and then, by solubilisation and change of pH, the protein contaminants, and finally purified by ultrafiltration to reduce the volume and the PEG content, then carrying out an optional virus filtration and subsequent concentration [to a protein value of 5% or 10%].